IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of
Caulkett et al.

Atty. Ref:. **056291-5025**

Serial No. **09/674,559**

Group **1624**

Filed: **April 1, 2001**

Examiner: **Raymond**

For: **HETEROCYCLIC DERIVATIVES**

DECLARATION

I, Peter William Rodney Caulkett, of 32A Lime Grove, Macclesfield, Cheshire, SK10 1LX, UK hereby declare as follows:

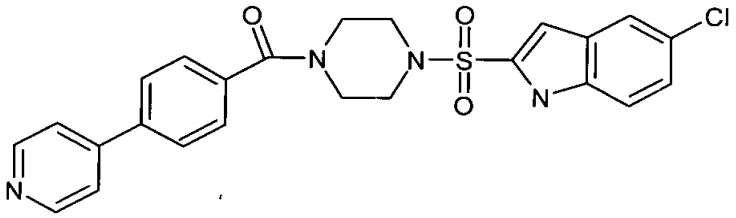
1. I am a Chartered Chemist (CChem) and am a Member of the Royal Society of Chemistry.

2. Since 1972, I have been working as a research chemist within Zeneca Pharmaceuticals. During that time, I have been working as a research chemist in various project areas including projects working on peripheral ischaemia, topical anti-inflammatory compounds, as well as Factor X and Factor VII inhibitors for treatment of diseases such as thrombosis. I am currently a team leader in a diabetes project. In 1999, I was working on a Factor Xa project. I am the inventor of the subject application. I understand that the invention of the application is regarded as being obvious over US Patent No. 6,300,330.

3. US Patent No. 6,300,330 describes a broad range of compounds, which are inhibitors of Factor Xa. These compounds have a number of features in common with the compounds of the present application. However, the ring represented by Q in US Patent No. 6,300,330 can be a wide range of variables, including aromatic carbocyclic and heterocyclic ring systems. By far the most widely exemplified group at this position was an aromatic carbocyclic group, and particularly naphthyl. In the present case however, the compounds can have an indole ring at this position.

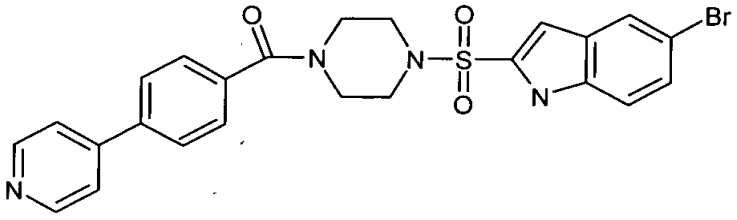
4. The compounds of the present application were prepared either by me or under my supervision. When the compounds had been prepared, they were submitted for biological screening in accordance with usual company practice. The compounds were tested for Factor Xa inhibitory activity using the method of test a) and test b) described in the present application and also in US Patent No, 6,300,330.

The results for the compounds of the present application, were recorded as follows:
Example 3 of present application, of formula:



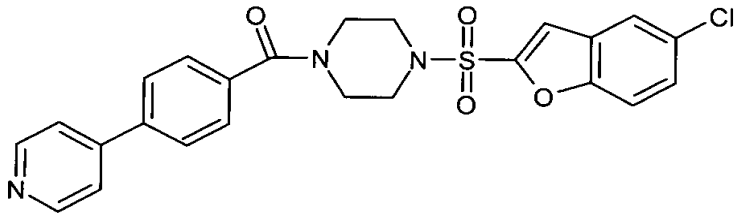
had a Factor Xa IC50 of 0.005μM (average of 3 measurements) in test a), and an IC50 human PT of 12μM (average of 2 measurements) in test b.

Example 9 of the present application of formula:



had a Factor Xa IC50 of 0.005μM in test a), and an IC50 human PT of 15μM (average of 2 measurements) in test b).

5. In contrast, the data recorded on the company database from a similar test conducted in Example No. 12 of US Patent No. 6,300,330 (which is also Example 1 of the present application) of the following structure:



had a Factor Xa IC50 of 0.057μM (average of 2 measurements) in test a), and an IC50 human PT of 35μM (average of 2 measurements) in test b.

6. It appears from these results that that the compounds of the present application are more potent than this prior art compound. Such increased potency was unexpected.

7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

Peter William Rodney Caulkett ..... 3rd Nov 2003

Peter William Rodney Caulkett ..... Date